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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,089	06/26/2003	Miklos Gratzl	CWR 2 0282	8107

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EXAMINER	
NOGUEROLA, ALEXANDER STEPHAN	
ART UNIT	PAPER NUMBER
1753	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/980,089	GRATZL ET AL.	
	Examiner	Art Unit	
	ALEX NOGUEROLA	1753	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-15 and 29-31* is/are allowed.

6)☐ Claim(s) *16-19,21,22,24,25 and 27* is/are rejected.

7)☒ Claim(s) *20, 23, 26, 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Objections and Rejections pending since the Office action of September 07, 2006

1. All previous objections and rejections are withdrawn.

Claim Rejections - 35 USC § 103

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 16, 22, 24, 25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yi et al. ("Continuous in Situ Electrochemical Monitoring of Doxorubicin Efflux from Sensitive and Drug-Resistant Cancer Cells," Biophysical

Journal, volume 75, November 1998, 2255-2261) ("Yi") in view of Belmont et al. (US 6,900,043 B1) ("Belmont").

Addressing claim 16, Yi discloses an apparatus for measuring efflux of a chemical from a biological cell, or a population of cells (abstract), the apparatus including

a substrate (glass cover slip) having a surface which receives the cell (Figure 1A);

a medium on the substrate (Figure 1B);

an electrochemical monitoring system which measures an electrochemical property of the medium surrounding the cell, the property being related to a concentration of the chemical in the medium (abstract and Figure 1), the apparatus characterized by the electrochemical system including a carbon electrode which extends to the attachment region for measuring the electrochemical property of the medium surrounding the cell (Figure 1).

Yi does not mention a surface of the substrate having at least one attachment region to which the cell or population of cells attaches, the region being surrounded by a resistant region which resists attachment of cells. Belmont teaches encircling cells on a substrate with a hydrophobic pen. See col. 43:42-57. It would have been obvious to one with ordinary skill in the art at the time of the invention to create a hydrophobic region on the substrate which resists attachment of cells as taught by Belmont in the invention of Yi because this will prevent the cells from falling off or moving off the slide.

In Yi the carbon electrode does not extend at an angle relative to the attachment region, but extends horizontally and is parallel to the attachment region (Figure 1). In Yi the substrate is a substantially planar shallow container. However, barring evidence to the contrary, such as unexpected results, the angle at which the carbon electrode is held just depends on the shape of the substrate. No criticality has been shown relating to whether the carbon electrode extends at an angle or not. At the time of the invention cells were held in a variety of containers of different shapes and sizes. For example, a cylindrical or conical shaped container such as test tube, vial, or microtitre well was commonly used to hold cells. With such containers the carbon electrode (and counter and reference electrode) would have to extend at an angle relative to the attachment region. Yi clearly contemplates using the carbon electrode in different environments as the carbon electrode (and reference electrode and counter electrode) is not integral with or permanently affixed to the substrate and Yi discloses the carbon electrode may be used for in situ monitoring (Figure 1 and last paragraph of the article).

Addressing claim 22, for the additional limitation of this claim note the separated cells in Figure 1 of Yi.

Addressing claim 24, Yi does not mention having the surface include "a plurality of attachment regions which each attracts a single cell or group of cells, each attachment region having an associated working electrode positioned adjacent the attachment region." However, barring evidence to the contrary, such as unexpected

results, this is just multiplication of parts for a multiplied effect. By just increasing the surface area of the surface a plurality of cells or groups of cells can be attached to the surface. This would allow, along with the plurality of working electrodes, simultaneous measurements to made on different cells at the same time. Such measurements may simply be redundancy for statistical purposes.

Addressing claim 25, for the additional limitation of this claim see Figure 1A of Yi.

Addressing claim 27, Yi discloses a method of measuring efflux of a chemical from a biological cell (abstract), or a population of cells (abstract), the method including introducing the chemical to the cell and measuring an electrochemical property of a medium surrounding the cell or population of cells (abstract and Figures 1 and 4), the property being related to a concentration of the chemical in the medium (abstract and Figure 4), the method characterized by

positioning the cell or population of cells on a surface of a substrate by attachment of the cell or cell population to an attractive region of the substrate which permits attachment (Figure 1);

the electrochemical system including a carbon electrode which extends to the attachment region for measuring the electrochemical property of the medium surrounding the cell (Figure 1).

Yi does not mention having the attractive region of the substrate being surrounded by a region which resists attachment of cells.

Belmont teaches encircling cells on a substrate with a hydrophobic pen. See col. 43:42-57. It would have been obvious to one with ordinary skill in the art at the time of the invention to create a hydrophobic region on the substrate which resists attachment of cells as taught by Belmont in the invention of Yi because this will prevent the cells from falling off or moving off the slide.

In Yi the carbon electrode does not extend at an angle relative to the attachment region, but extends horizontally and is parallel to the attachment region (Figure 1). In Yi the substrate is a substantially planar shallow container. However, barring evidence to the contrary, such as unexpected results, the angle at which the carbon electrode is held just depends on the shape of the substrate. No criticality has been shown relating to whether the carbon electrode extends at an angle or not. At the time of the invention cells were held in a variety of containers of different shapes and sizes. For example, a cylindrical or conical shaped container such as test tube, vial, or microtitre well was commonly used to hold cells. With such containers the carbon electrode (and counter and reference electrode) would have to extend at an angle relative to the attachment region. Yi clearly contemplates using the carbon electrode in different environments as the carbon electrode (and reference electrode and counter electrode) is not integral with or permanently affixed to the substrate and Yi discloses the carbon electrode may be used for in situ monitoring (Figure 1 and last paragraph of the article).

4. Claims 17-19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yi et al. ("Continuous in Situ Electrochemical Monitoring of Doxorubicin Efflux from Sensitive and Drug-Resistant Cancer Cells," Biophysical Journal, volume 75, November 1998, 2255-2261) ("Yi") in view of Belmont et al. (US 6,900,043 B1) ("Belmont") as applied to claims 16, 22, 24, 25, and 27 above, and further in view of Earles et al. ("Rotating Disk Electrode Voltammetric Measurements of Dopamine Transporter Activity: An Analytical Evaluation," Analytical Biochemistry 264, 191-198 (1998)) ("Earles") and the CAPLUS abstract for "Growth behavior of Chinese hamster ovary cells in a compact loop bioreactor: 1. Effects of physical and chemical environments," Journal of Biotechnology (1990), 15, 101-11) ("Kurano").

Addressing claim 17, Yi does not mention a source of oxygen containing gas which supplies oxygen to the medium to increase a signal strength of the electrochemical property.

Earles discloses a method of measuring efflux of a chemical from a cell or a

population of cells (abstract), the method including measuring an electrochemical property of a medium surrounding the cell with an electrochemical system which includes a working electrode and a reference electrode, the property being related to a concentration of the chemical in the medium (abstract and Figure 1). Earles further teaches adding oxygen to the medium (*Saturation of Oxygen in the Incubation Chamber* on page 196 of Earles). It would have been obvious to one with ordinary skill in the art at the time of the invention to add oxygen as taught by Earles in the invention of Yi (and thus provide a source of oxygen containing gas) because as taught by Earles the oxygen will keep the cells or tissues viable (Chinese hamster ovary cells also consume oxygen as shown by the Kurano abstract). Although Yi as modified by Earles does not mention that the oxygen is to increase a signal strength of the electrochemical property this is inherent because if this oxygen was not provided some cells would likely die or deteriorate, thus lowering the signal strength.

Addressing claim 18, that the source of oxygen containing gas comprises a container of substantially pure oxygen under pressure is implied because the oxygen is a stream of 95%O_2 – 5% CO_2. See *Saturation of Oxygen in the Incubation Chamber* on page 196 of Earles.

Addressing claim 19, for the additional limitation of his claim see Figure 1 in Yi.

Addressing claim 21, note that Yi states, "Further development of this technique can lead to virtually continuous monitoring of drug efflux from a few cells or even a single cancer cells ..." and "This infers that it may be feasible to detect drug efflux from a single cancer cell with the techniques proposed in this work." See, respectively, the third full paragraph in the first column on page 2256 and fourth full paragraph on page 2260. Additionally, Yi discloses that monitoring of as few as four cells is possible. See the third full paragraph in the first column on page 2260. Thus, barring a contrary showing, having the attachment region of Yi as modified by Earles and Kurano sized for attachment of only one cell is just an obvious variant of monitoring a few cells.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 27 recites the limitation "the electrochemical system" in line 10. There is insufficient antecedent basis for this limitation in the claim.

Allowable Subject Matter

7. Claims 1-15, and 29-31 are allowed.

8. Claims 20, 23, 26, 28 and are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Final Rejection

9. Applicant's amendment necessitated the new ground of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEX NOGUEROLA whose telephone number is (571) 272-1343. The examiner can normally be reached on M-F 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NAM NGUYEN can be reached on (571) 272-1342. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Alex Noguerola
Primary Examiner
AU 1753
April 12, 2007